clinical recommendations

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Newly and relapsed epithelial ovarian carcinoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

The crude incidence of ovarian cancer in the European Union is 18, the mortality is 12/100 000 women/year. The median age at diagnosis is 63 years. The incidence increases with age and peaks in the eighth decade.

diagnosis

The definitive diagnosis of epithelial ovarian cancer requires a surgical specimen. Pathological diagnosis should be made according to the WHO classification. Established subtypes are: serous, mucinous, endometrioid, clear cell, transitional cell, mixed and undifferentiated carcinomas.

staging and risk assessment

Surgical staging requires a median laparotomy with a thorough examination of the abdominal cavity according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification guidelines. If disease appears confined to the ovary, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum, an infracolic omentectomy and sampling or dissection of para-aortic and pelvic nodes are required in addition to peritoneal washings.

Surgery should be performed by an appropriately trained gynaecologic oncologist with experience in the management of ovarian cancer [III, B].

Staging is described using the FIGO and American Joint Committee on Cancer (AJCC) classification as in Table I.

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This set of recommendations applies to invasive epithelial ovarian carcinoma; the management of tumors of low malignant potential ('borderline') is not covered here.

Established favorable prognostic factors besides surgical stage are: small tumor volume (before and after surgery), younger age, good performance status, cell type other than mucinous or clear cell, well-differentiated tumor and absence of ascites. Low grade, absence of dense adhesions, minimal ascites, subgroups a/b versus c and cell type other than clear cell are considered good prognostic factors for patients with stage I disease.

Before surgery and/or chemotherapy, patients should have a CT scan of the abdomen and pelvis, chest X-ray, serum CA125, complete blood count and differential, and biochemistry for renal and hepatic function. The routine use of FDG-PET–CT for initial staging is not recommended.

treatment plan

The selection of the type of surgery and postoperative chemotherapy depends upon the stage and other clinicopathological prognostic factors.

early stage disease, FIGO stage I and IIa

Surgery should involve total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, random peritoneal biopsies including the paracolic gutters and at least pelvic/para-aortic lymph node sampling performed as described above. In younger patients with localized, unilateral tumors (stage I) and favorable histology, who wish to conserve fertility, unilateral salpingo-oophorectomy may not be associated with a high risk of recurrence. Wedge biopsy of the contralateral ovary should be performed, if the contralateral ovary is not normal on inspection. FIGO stage I tumors with dense adhesions to other pelvic structures should be 'upstaged' and treated as FIGO II tumors, as the relapse rate appears to be similar [IV].

FIGO stage Ia/b, well-differentiated, non-clear cell histology: surgery alone is adequate [I, A]. FIGO stage Ia/b poorly differentiated, densely adherent, clear cell histology and all grades FIGO stage Ic and IIA: optimal surgery and staging should be performed, and adjuvant chemotherapy considered [I, A].

Consider three cycles of carboplatin AUC 5–7 mg/ml/min + paclitaxel 175 mg/m^2/3 h for non-serous early stage ovarian

Table 1. Staging using the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and American Joint Committee on Cancer (AJCC) classification

Stage I	Limited to ovaries
Ia	One ovary
Ib	Both ovaries
Ic	Ruptured capsule, surface tumor or positive washings[a]
Stage II	Pelvic extension
IIa	Uterus, tube(s)
IIb	Other pelvic tissue
IIc	Positive washings, ascites
Stage III	Abdominal extension and/or regional lymph nodes
IIIa	Microscopic peritoneal metastases
IIIb	Macroscopic peritoneal metastases ≤2 cm
IIIc	Macroscopic peritoneal metastases >2 cm and/or regional lymph nodes
Stage IV	Distant metastases outside peritoneal cavity

[a]For the estimation of the prognosis, this includes iatrogenic intraoperative rupture

cancer if combination therapy is to be used [II, B]. Otherwise, six cycles of carboplatin ± paclitaxel would seem appropriate.

advanced disease, FIGO stage IIb–IIIc

Surgery should include total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy, with staging biopsies performed as described. Up-front maximal surgical effort at cytoreduction with the goal of no residual disease should be undertaken.

The recommended standard chemotherapy for advanced ovarian carcinoma, stages IIb–IIIc is carboplatin AUC 5–7 mg/ml/min ± paclitaxel 175 mg/m^2/3 h every 3 weeks for six cycles. Patients should receive optimal doses of chemotherapy based on measured glomerular filtration rate (GFR) and actual body weight; dose reductions for obesity are discouraged [III].

If initial maximal cytoreduction was not performed, interval debulking surgery should be considered in patients responding to chemotherapy, or showing stable disease [II, B]. Interval debulking surgery should ideally be performed after three cycles of chemotherapy, followed by three further cycles of chemotherapy.

There is no evidence of a survival benefit for 'second-look' surgery following completion of chemotherapy in patients whose disease appears to be in complete remission. Such procedures should only be undertaken as part of a clinical trial. Likewise, the value of secondary tumor reduction at the time of second-look laparotomy is not clear.

Intraperitoneal chemotherapy should be considered an option in centers where the expertise exists.

Neoadjuvant chemotherapy for patients considered initially not optimally resectable for either tumor or patient-related factors is a viable alternative strategy; however, available data suggest that the survival outcome may be inferior to that from successful primary surgery followed by chemotherapy.

advanced disease, FIGO stage IV

Patients with stage IV disease may obtain a survival advantage from being maximally surgically cytoreduced at initial laparotomy [III, B], although randomized trials have not addressed this question.

Younger patients with good performance status, pleural effusion as the only site of disease outside the abdominal cavity, small volume metastases and no major organ dysfunction should be considered for surgery as outlined for FIGO stage IIb–III disease.

If surgery is not planned, the diagnosis should be confirmed by biopsy and chemotherapy administered as recommended above for FIGO stage IIb–IIIc disease.

response evaluation

CA125 levels during chemotherapy correlate with tumor response and with survival [III, A]. Serum CA125 should be measured at regular intervals during chemotherapy (e.g. before each cycle).

For patients with abnormal CT scan at baseline, this should be repeated after cycle 6 unless there is evidence (e.g. CA125 levels not falling) of non-responding disease; in this case an earlier CT scan would be indicated. Patients with normal CT scans at baseline do not need further CT scans, provided there is no clinical or biochemical indication of disease progression. An interim CT scan after three cycles of chemotherapy should be considered for a patient who is negative for serum CA125, or for whom interval debulking surgery is being considered.

Current data do not support a recommendation of maintenance/consolidation treatment beyond six cycles; however, the data for 12 months of paclitaxel maintenance may be discussed with patients with respect to the potential improvement observed in PFS [II, C], especially in patients with low concentrations of CA125 [III, B]. Patients with a partial response (or elevated CA125) after six cycles of chemotherapy but continuing evidence of response by CA125 can be considered for a further three cycles of the same chemotherapy [V, D].

follow-up

History, physical examination including pelvic examination every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5 or until progression is documented.

CA125 can accurately predict tumor relapse [I, A], and may be performed at follow-up visits. It is unknown, however, whether the early detection of recurrence by CA125 offers any advantage. CT scans should be performed if there is clinical or CA125 evidence of progressive disease. FDG-PET–CT scans may be superior to CT scans in detecting small volume operable relapses [III, B].

recurrent disease

Patients with long intervals (>1 year) from primary surgery should be considered for surgical resection of recurrent disease [III, A]. Patients with long intervals (>6 months) from initial

chemotherapy should be offered platinum-based combination chemotherapy (carboplatin + paclitaxel, carboplatin + gemcitabine) [I, A]. For patients with short treatment-free intervals and with second and later recurrences, palliative chemotherapy with pegylated liposomal doxorubicin, gemcitabine or topotecan should be considered [II, B].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

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